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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Application Number: 09/707,000
Filing Date: November 06, 2000
Appellant(s): WOLFF ET AL.

Mark Johnson
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 6-14-07 appealing from the Office action mailed 8-18-04.

(1) Real Party in Interest

A statement identifying by name the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

The following are the related appeals, interferences, and judicial proceedings known to the examiner which may be related to, directly affect or be directly affected by or have a bearing on the Board's decision in the pending appeal:

09/707117

(3) Status of Claims

The statement of the status of claims contained in the brief is correct.

(4) Status of Amendments After Final

No amendment after final has been filed.

(5) Summary of Claimed Subject Matter

The summary of claimed subject matter contained in the brief is correct.

(6) Grounds of Rejection to be Reviewed on Appeal

The following grounds of rejection are not presented for review on appeal because the examiner has withdrawn them.

New Matter

The new matter rejection regarding the phrase "sufficient pressure" in claim 1 has been withdrawn in view of applicants' arguments.

Indefiniteness

The indefiniteness rejection of claim 1, step c), regarding the phrase "to occlude blood flow to said limb" has been withdrawn because it must relate to "sufficient pressure." Therefore, the "sufficient pressure" must "occlude blood flow to said limb." It is noted that step c) of claim 1 would be more clear written as "applying pressure in an amount sufficient to occlude blood flow to said limb".

The indefiniteness rejection regarding the metes and bounds of the term "cuff" (claims 35, 36) has been withdrawn. The specification states: "The term cuff means a device for impeding blood flow through mammalian intemal blood vessels. However, for purposes of the claims, cuff refers specifically to a device applied exterior to the mammal's skin and touches the skin in a non-invasive manner" (pg 5, lines 13-15). While the specification provides two definitions for "cuff," the specification clearly states the term "cuff" as claimed is limited to "a device applied exterior to the mammal's skin and touches the skin in a non-invasive manner." Any definition of "invasive" known at the time of filing to those of skill may have been applied to the term "invasive" in the specification.

Double Patenting

The rejection of claims 1-3, 37 and 39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1 of U.S. Patent No. 6,379,966 in view of the disclosure of '966 has been withdrawn. Applicants argue

'966 did not teach applying a non-invasive cuff. Applicants' argument is not persuasive. The claims in the instant application are not limited to applying a non-invasive cuff. However, the claim 1 is limited to "applying a device for impeding blood flow to the surface of the skin" and claim 39 is limited to pressure that "is applied to the skin of the limb by a device external to the skin of said mammal." '966 suggested increasing the permeability of blood vessels by "increasing the intravascular hydrostatic (physical) pressure" (sentence bridging col. 2-3). "For example an afferent vessel supplying an organ is rapidly injected and the efferent vessel draining the tissue is ligated transiently." (col. 7, lines 20-22). '966 did not apply a device "to the surface of the skin" or apply pressure "to the skin of the limb by a device external to the skin of said mammal."

The rejection of claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 33-36 and 39 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over the claims of Application No. 09/917154 has been withdrawn because application '154 has been abandoned.

The following grounds of rejection remain for review on appeal:

I. Whether claims 1-3, 6-9, 11-14, 16-22, 24-26, 29-31, 34-36 and 39 are unpatentable under 35 U.S.C. first paragraph because they contain new matter.

a) Whether "syringe needle" is new matter

b) Whether "impeding blood flow to the surface of the skin" is new matter

II. Whether claims 1-3, 6-9, 11-14, 16-22, 24-26, 29-31, 34-36 and 39 are unpatentable under 35 U.S.C. first paragraph because they lack enablement.

a) Whether the specification enables injecting a polynucleotide distal to a tourniquet using an injection devise inserted into the limb proximal to the tourniquet as encompassed by the claims.

b) Whether the specification enables delivering viral vectors to skeletal muscle cells distal to occlusion as claimed

c) Whether the specification enables using any polynucleotide encoding a protein as broadly claimed

d) Whether the specification enables delivering a polynucleotide without obtaining protein expression

III. Whether claims 1-3, 6-9, 11-14, 16-22, 24-26, 29-31, 34-36 and 39 are unpatentable under 35 U.S.C. second paragraph because they are indefinite.

a) Whether the phrase "applying a devise for impeding blood flow to the surface of the skin" in claim 1, step b), is clear.

b) Whether the metes and bounds of "sufficient pressure" required "to occlude blood flow to said limb" in claim 1, step c) are unclear.

c) Whether the phrase "said occlusion" in claim 1, step d) lacks antecedent basis.

d) Whether the claims recite all the steps of the method.

e) Whether the phrase "wherein function of the limb is not affected by inserting the injector, applying pressure to the vessel, and injecting the solution" is clear.

IV. Whether claims 1, 3, 34-36 and 39 are unpatentable under 35 U.S.C. 102 as being anticipated by Milas (Clin. Cancer Res., 1997).

V. Whether claims 1-3, 6-9, 11-14, 16-22, 24-26, 29-31, 34-36 and 39 are unpatentable under the judicially created doctrine of obviousness-type double patenting over US Patent application 09/707,117.

(7) Claims Appendix

A substantially correct copy of the appealed claims appears on page 15-17 of the Appendix to the appellant's brief. The minor errors are as follows: the status identifier in claim 1 is missing and in claim 39 is "currently amended" on pg 15-17 of the Appendix to the appellant's brief; however claims 1 and 39 should each be labeled "previously presented."

Claim 1, step a, on pg 15-17 of the Appendix to the appellant's brief has been amended but not marked to delete the word "a" before the word "an" to overcome the objection to claim 1, step a.

(8) Evidence Relied Upon

The following ground(s) of rejection are applicable to the appealed claims:

Miller, 1995, FASEB J., Vol. 9, pages 190-199;

Deonarain, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69;

Verma, Sept. 1997, Nature, Vol. 389, pg 239-242;

Crystal, 1995, Science, Vol. 270, pg 404-410; pg 409;

Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203);

Ye (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627);

Draijer-van der Kaaden (US Patent 6,495,131);

Von der Leyen (9-20-99, Human Gene Therapy, Vol. 10, pg 2355-2364);

Budker (1998, Gene Therapy, Vol. 5, pg 272-276); and

Wolff (US Patent 6,265,387, July 24, 2001).

(9) Grounds of Rejection

Claim Objections

Numerous claim objections remain from the final office action and are presented here only for completeness sake. They are not for review on appeal:

The phrase "inserting an injector selected from the group consisting of a syringe needle and catheter" in claim 1 can be stated more clearly as "inserting a needle or catheter".

The objection to claim 1, step a) regarding the phrase "inserting an injector... ...into a an artery in said limb" having "a" and "an" together has been withdrawn in view of the unmarked amendment in the Appendix to appellant's brief on pg 15-17.

In claim 1, step a) the phrase "inserting an injector... ...into an artery in said limb" should be "inserting an injector... ...into an artery in a limb of a mammal" to be more clear and to parallel the language in the preamble.

Claim 1, step c), would be more clear written as "applying pressure in an amount sufficient to occlude blood flow to said limb".

In claim 1, steps b) and c) would be more clear if they were combined. Step c) limits how the device in step b) is applied. Applying pressure using the device in step c) is not really a separate step. It limits the function of the cuff in step b). Simplify the steps into one step, e.g. applying a device to the skin of said limb such that blood flow to the limb is occluded.

Use of the term "impeding" (step b) and "occluding" (step c) together in claim 1 is confusing.

In claim 35, delete "surrounding said limb" to be more clear.

The phrase "inserting an injector selected from the group consisting of a syringe needle and catheter" in claim 39 can be stated more clearly as "inserting a needle or catheter".

In claim 39, step a) the phrase "inserting an injector... ...into a blood vessel in said limb in the mammal" should be "inserting an injector... ...into an artery in a limb of a mammal" to be more clear and to parallel the language in the preamble.

The phrase "applying pressure..." in claim 39, step a) is a separate step and should be step b). This phrase can also be simplified, e.g. --applying a device to the skin of said limb such that blood flow through the blood vessel is occluded--.

The phrase labeled "c) wherein function..." in claim 39 is not a step. The phrase is describing a functional limitation of the steps and does not require an active step.

Claim Rejections - 35 USC ' 112

New Matter

I. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 stand rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claims contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventors, at the time the application was filed, had possession of the claimed invention for reasons of record.

a) **New matter of "syringe needle"**

The new phrase "syringe needle" in claim 1 and 39 does not have support on pg 31, which only teaches a needle, or on pg 23 or 25, which only describes a catheter. The needle on pg 31 could have been attached to a tube and not a syringe. Therefore, the "syringe needle" as claimed is new matter because it has a narrower scope than a "needle" on pg 31 as originally filed.

b) **New matter of "impeding blood flow to the surface of the skin"**

The phrase "impeding blood flow to the surface of the skin" in claims 1 and 39 does not have support in the specification as originally filed and is new matter. Pg 3, lines 8-11, and pg 5, lines 5-24, describe "impeding interior blood flow" to the limb by "applying a tourniquet over [sic] the skin." The genus of "impeding blood flow to the surface of the skin" is not the same as "impeding interior blood flow" as expressly taught on pg 3, lines 8-11, or to the limb as implicitly taught on pg 5, lines 7-8, which discusses limb injections and impeding blood flow.

Enablement

II. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 remain rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method comprising applying a tourniquet to the limb of a mammal such that blood flow of a blood vessel in the limb is occluded and administering naked DNA to said blood vessel distal to the occlusion, wherein said DNA comprises a nucleic acid sequence encoding a protein operably linked to a promoter and wherein said protein is expressed to detectable levels in skeletal muscle cells of said limb distal to the occlusion, does not reasonably provide enablement for 1) applying a tourniquet to a limb; inserting an injector into an artery of the limb proximal to the tourniquet, and injecting a polynucleotide through the injector distal to the tourniquet; 2) inserting an injector into an artery of a limb; applying a tourniquet to the limb; and injecting an adenoviral vector through the injector distal to the tourniquet such that the adenoviral vector is delivered to skeletal muscle cells distal to the tourniquet; 3) administering any polynucleotide that does not encode protein operably linked to a promoter, or 4) merely "delivering a polynucleotide" with obtaining expression of the protein encoded by the polynucleotide. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

a) **Enablement of injecting a polynucleotide distal to a tourniquet using an injection devise inserted devise into the limb proximal to the tourniquet.**

For this rejection, a "tourniquet" refers to the "devise for impeding blood flow" in claims 1 and 39.

Claims 1 and 39 encompass applying a tourniquet to a limb; inserting an injection devise into an artery of the limb either proximally or distally to the tourniquet; and injecting a polynucleotide into the artery distal to the tourniquet. However, the specification does not teach how to apply a tourniquet to a limb; insert an injection devise into the limb proximal to the tourniquet; and inject a polynucleotide distal to the tourniquet. Claims 1 and 39 are not limited to inserting the injector distally to the applied pressure.

The specification does not enable one of skill to insert an injector into an artery of a limb proximally to the tourniquet and inject the polynucleotides distally to the tourniquet. In this scenario, the tourniquet separates the injector from the "distal" skeletal muscle cells of the limb and would prevent injecting distal to the applied pressure as claimed. The specification does not teach any means of inserting an injector proximal to a tourniquet and passing the injector under the tourniquet so that the polynucleotide could be injected into the artery distal to the tourniquet. It would require one of skill undue experimentation to determine how to do so. Accordingly, one of skill could not insert an injector proximally to the tourniquet and inject a polynucleotide distal to the tourniquet as encompassed by the claims. The claims should be limited to inserting the injector distal to tourniquet.

b) **Enablement of delivering adenoviral vectors to skeletal muscle cells**

For this rejection, it is assumed Milas does not obtain "delivery" of adenovirus to skeletal muscle cells because β-gal was not be detected in skeletal muscle cells. This interpretation is different than the one in the 102 rejection.

Breadth of claims

Claims 1 and 39 are basically drawn to applying a devise for impeding blood flow to a limb; applying sufficient pressure against the limb so that blood flow to said limb is occluded; inserting an injection devise into a blood vessel of the limb; and injecting a polynucleotide into the blood vessel distal to the occlusion thereby delivering the polynucleotide to a skeletal muscle cells distal to the occlusion.

Claims 1 and 39 encompass using a polynucleotide that is a viral vector. Claim 3 specifically requires the polynucleotide is a viral vector.

Claim 1 requires "applying a device for impeding blood flow to the surface of the skin of said limb; applying sufficient pressure against said limb with said device to occlude blood flow to said limb."

Claim 39 requires applying "pressure to the blood vessel wherein the pressure occludes blood flow through said blood vessel and is applied to the skin of said limb by a device external the skin of said mammal".

Claims 1 and 39 use open claim language and encompass occluding blood flow using applied pressure while allowing some blood flow to occur. Claims 1 and 39 are not limited to occluding all blood flow or to preventing outflow of blood.

As such, claims 1 and 39 encompass applying a tourniquet to a leg wherein the tourniquet occludes blood flow between the limb and the rest of the body while at the same time using a perfusion pump that allows blood flow between the limb and the perfusion pump.

State of the art and level of skill

It was well know and remains well known that the conditions required to target a vector to desired tissues of interest in vivo was unpredictable as supported by numerous teachings available in the art (Miller of record, 1995, FASEB J., Vol. 9, pages 190-199; Deonarain of record, 1998, Expert Opin. Ther. Pat., Vol. 8, pg 53-69; pg 53, 1st ¶, pg 65, 1st ¶, under Conclusion section; Verma of record, Sept. 1997, Nature, Vol. 389, pg 239-242, see entire article, pg 240, sentence bridging col. 2 and 3; and Crystal of record, 1995, Science, Vol. 270, pg 404-410; pg 409).

More specifically, Milas of record (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) shows that the conditions required to obtain protein expression in skeletal muscles of a limb using a viral vector were unpredictable. Milas applied a tourniquet to the leg of a rat and injected adenoviral particles to the femoral artery and vein distal to the tourniquet using a perfusion pump (pg 2198, Fig. 1A and B, see legend and tourniquet in Fig. 1A; pg 2198, "Operative Technique"; pg 2199, Fig. 2). Applying a tourniquet as described by Milas also meets the "devise for impeding blood flow" or "applying pressure... ...to occlude blood flow to [through] said limb" because the limitation uses open language and does not exclude impeding blood flow between the leg and the rest of the body while using a perfusion pump that allows blood flow between the leg and the perfusion pump; the claims are not limited to impeding all blood flow into and out of the leg. Therefore, the steps of applying a tourniquet and injecting an adenoviral vector taught by Milas are within the metes and bounds of the steps in claims 1 and 39. However, the method of Milas did not result in delivery to skeletal

muscle cells distal to the occlusion as claimed because LacZ expression was not detectable in skeletal muscle cells distal to the applied pressure (pg 2201, col. 2, 1st full ¶). Therefore, one of skill would have recognized that not applying a tourniquet to a limb and injecting an adenovirus into a blood vessel distal to the occlusion would not result in delivery of the adenovirus to skeletal muscle cells as claimed.

Ye of record (March 1, 2000, Human Gene Therapy, Vol. 11, pg 621-627) administered adenoviral particles encoding LacZ retroorbitally while the portal vein/artery was occluded with clamps; the method did not result in expression in skeletal muscle (pg 623, col. 2). Thus, while Ye did not administer the adenoviral particles to the limb or apply pressure to the skin as claimed, Ye supports the fact that one of skill would not necessarily know how to deliver adenoviral vectors to a blood vessel and obtain expression in skeletal muscle cells (pg 621, 1st full paragraph).

Examples and Teachings in the specification

Example 1 in the specification teaches making an incision in the limb of a monkey, placing a catheter into an artery anterogroadely, impeding blood flow using a sphygmomanometer cuff surrounding the limb proximal to the injection site. The sphygmomanometer was inflated and papaverine was injected into the catheterized artery followed by naked plasmid DNA encoding a marker protein operably linked to a promoter (pg 23, lines 13-26). Expression was obtained in skeletal muscles (pg 25, line 29, through pg 28, line 3). Example 8 on pg 31 does not require applying pressure to the skin as claimed. The method in Example 9 cannot be determined because it merely

states the solution was injected "as described in Examples above" without stating the method of Example 1 was used.

The specification suggests using a viral vector, specifically an adenoviral vector (pg 15, line 14). However, the specification does not provide any teachings for one of skill to overcome the teachings of Milas or provide any examples of injecting an adenovirus while applying a sphygmomanometer cuff or tourniquet to the skin.

Amount of experimentation

One of skill would recognize that the step occluding blood flow as broadly claimed by the steps of Milas would not result in expression in skeletal muscle cells as claimed if the polynucleotide was an adenoviral vector. Given the breadth of the claims taken with the teachings of Milas and the lack of teachings in the specification regarding how to overcome the teachings of Milas and obtain expression in skeletal muscle cells using adenovirus, it would have required one of skill undue experimentation to determine how to perform the steps required to use an adenovirus and obtain expression in skeletal muscle cells as claimed. While non-operative embodiments are allowed in a claim, steps that are not enabled in the specification are not. The claims do not exclude using a perfusion pump while applying a tourniquet. No amount of experimentation would allow one of skill to obtain expression of an adenovirus in skeletal muscle cells by applying a tourniquet while using a perfusion pump as encompassed by the claims.

c) **Enablement of polynucleotides encoding a protein without a promoter**

While pg 14, lines 14-30, teaches the polynucleotide may be DNA or RNA, the elected subject matter is drawn to a method of delivering a polynucleotide encoding a protein and excludes polynucleotides that block protein expression (pg 2 of office action sent 7-30-02). Claims 1 and 39 are only being examined as they relate to delivering a polynucleotide encoding a protein. Pg 14, lines 31-32, teaches the polynucleotide expresses an exogenous nucleotide sequence. The specification only teaches polynucleotides encoding a protein as being operably linked to a promoter. The specification does not enable delivering polynucleotides encoding a protein in the absence of a promoter. Therefore, the claims should be limited to a polynucleotide encoding a protein operably linked to a promoter.

d) **Enablement of merely delivering a polynucleotide encoding a protein**

Claims 1 and 39 encompass delivering a polynucleotide to skeletal muscle cells without obtaining protein expression. The specification does not provide an enabled use for mere delivery of a polynucleotide to a skeletal muscle cell as claimed. For the delivery to have an enabled use, it must be expressed to detectable levels in the cell. Therefore, the claims should recite a final step of obtaining detectable levels of expression of the protein.

Indefiniteness

III. Claims 1-3, 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 remain rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

a) The phrase "applying a devise for impeding blood flow to the surface of the skin" in claim 1, step b), is unclear. It is unclear if applicants are attempting to limit where the blood flow has been impeded (to the surface of the skin) or if applicants are attempting to limit where the device is applied (to the surface of the skin). The phrase does not clearly set forth that the device is applied to the skin because "to the surface of the skin" may relate to the phrase "impeding blood flow" and not the phrase "applying a devise".

b) The metes and bounds of "sufficient pressure" required "to occlude blood flow to said limb" in claim 1, step c) is unclear. The specification and the art at the time of filing do not define the amount of pressure required to occlude blood flow as claimed. While the specification teaches a cuff or tourniquet may be applied to the skin to occlude blood flow, the amount of pressure required to occlude blood flow is unclear. Specifically, it is unclear if the mere application of the cuff or tourniquet is "sufficient pressure" "to occlude blood flow to said limb", if any external pressure applied to the cuff or tourniquet is "sufficient pressure" "to occlude blood flow to said limb" or if a specific amount of external pressure applied to the cuff or tourniquet is "sufficient pressure" "to occlude blood flow to said limb" as claimed.

c) The phrase "said occlusion" in claim 1, step d) lacks antecedent basis. Literal antecedence is required when using the term "said." Therefore, "to occlude blood flow" in step c) is inadequate antecedent basis for the phrase. Especially in view of the fact that the "to occlude blood flow" is an intended use in step c) and may not occur.

d) Claim 39 remains unclear because it does not recite all the steps of the method; mere delivery of polynucleotides to cells does not have a disclosed use. The method

should result in expression of a protein in a cell. If applicants intend the claim to relate to therapy, the claim should result in a therapeutic effect.

e) Claim 39 step c remains indefinite because the phrase "wherein function of the limb is not affected by inserting the injector, applying pressure to the vessel, and injecting the solution" is written as an active step (e.g. performing an action, e.g. inserting, injecting, etc.) but is actually a functional limitation of the overall method. The steps of a) and b) are active steps. However, c) is not a step of the method and does not require action. The phrase in c) is a functional limitation of the overall method and not a separate active step as written. It is noted that the phrase in question refers to three active steps (inserting, applying and injection); however, the step of "applying" is written as part of the "inserting" step and not as a separate active step.

Claim Rejections - 35 USC ' 102

IV. Claims 1, 3, 34, 35 and 39 stand rejected under 35 U.S.C. 102(b) as being anticipated by Milas (Dec. 1997, Clin. Cancer Res., Vol. 3, pg 2197-2203) for reasons of record.

For this rejection, it is assumed Milas obtains mere "delivery" of adenovirus to skeletal muscle cells. This interpretation is different than the one in the enablement rejection (b).

Claims 1 and 39 use open language and encompass partially occluding blood flow to the limb.

Claims 1 and 39 use open language and encompass occluding blood flow to the limb using a tourniquet while using a perfusion pump that allows blood to flow to the limb.

Claims 1 and 39 do not require expressing a protein encoded by the polynucleotide or entry of the polynucleotide into skeletal muscle cells.

Milas administered adenoviral particles distally to a femoral artery and vein of a rat occluded using a tourniquet applied to the skin. The adenovirus was administered using a catheter using a perfusion pump (pg 2198, col. 2 "Operative Technique"; Fig. 1A, and caption; pg 2199, Fig. 2, showing the tourniquet site). The tourniquet occluded blood flow to the leg, which is all that is required of the claims.

Milas inherently delivers "the polynucleotides to the skeletal muscle cells" as claimed. While Milas did not obtain detectable β-gal staining in skeletal muscle cells (pg 2201, col. 2, lines 16-18), Milas described the process provided the entire leg with blood (pg 2200, Fig. 3), which reasonably implies that adenovirus-laden blood passed from the femoral artery into the muscular branches and was in contact with skeletal muscle cells. Milas also described inflammatory infiltrates in skeletal muscle (pg 2201, col. 2, lines 23-26), which reasonably implies that foreign material, i.e. adenovirus, had penetrated the skeletal muscle. Contacting adenoviral-laden blood with skeletal muscle cells as in Fig. 3 combined with the inflammatory infiltrates in skeletal muscle is equivalent to delivering adenovirus to skeletal muscle cells as claimed.

The limitation in claim 39 c) is met because Milas taught the mice recovered function of their legs (pg 2201, col. 1, lines 1-11).

Double Patenting

V. Claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 stand provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 of copending Application No. 09/707117 in view of the disclosure of '117. Although the conflicting claims are not identical, they are not patentably distinct from each other because they share overlapping scopes of applying a cuff or tourniquet to a limb so that blood flow to the limb is occluded and injecting polynucleotides into a blood vessel of the limb. The slightly different scope claimed in the instant application is readily apparent from the disclosure of '117 and could have been pursued in '117. The differences in scope are so slight as to be insignificant and do not represent patentably distinct subject matter.

(10) Response to Arguments

The declaration by Jon A. Wolff filed 6-14-06 was not argued under any specific rejection in the response filed 6-14-06 or in any of the appeal briefs. It is assumed the declaration was intended to address the enablement rejections and is considered in the response to applicants' arguments regarding enablement below.

I. **New Matter**

a) **"syringe needle"**

Applicants argue, "syringe needle" in claim 1, step a) is readily apparent from the "needle" on pg 31. Applicants' argument is not persuasive. A needle can be attached

to a syringe or a tube. It is not readily apparent that the "needle" on pg 31 was attached to a "syringe" as now claimed. Therefore, the scope of "syringe needle" as now claimed has a narrower scope than "needle" as originally contemplated in the specification as originally filed. Applicants' arguments acknowledge that "syringe" narrows the term "needle" (pg 4, lines 6-8); however, the narrow scope is not readily apparent from the needle on pg 31.

b) **"impeding blood flow to the surface of the skin"**

Applicants argue the phrase "impeding blood flow to the surface of the skin" is found on pg 3, lines 8-24 and pg 5, lines 5-24. Applicants argue a cuff; tourniquet or sphygmomanometer supports the phrase. Applicants' arguments are not persuasive. Applicants contemplated that the cuff or tourniquet impeded internal blood flow or blood flow to the limb but did not contemplate the tourniquet impeded blood flow to the surface of the skin as now claimed.

II. **Enablement**

a) **Injecting polynucleotides distal to tourniquet using a devise inserted proximal to the tourniquet**

Applicants argue the specification exemplified inserting a catheter into a blood vessel proximal to a tourniquet, pushing the catheter through the blood vessel to the distal side of the tourniquet and injecting polynucleotides distal to the tourniquet. Applicants' argument is not persuasive. No such example can be found. None of the examples in the specification described inserting a catheter proximal to a tourniquet and pushing the catheter to the distal side of the tourniquet.

b) **Enablement of delivering adenovirus to skeletal muscle cells**

Applicants' argue Miller, Deonarain, Verma and Crystal do not contemplate the process taught by applicants. Applicants argue they have made progress in the field of gene therapy, and overcome any unpredictability taught by Miller, Deonarain, Verma and Crystal. Applicants' argument is not persuasive. Miller, Deonarain, Verma and Crystal have been used to establish the state of the art at the time of filing – that DNA delivery to the tissue of interest was unpredictable. The claims encompass the method steps of Milas, which did not result in "delivery" of adenovirus to skeletal muscle cells as claimed because β-gal was not detected in skeletal muscle cells. The claims do not exclude occluding a blood vessel of a limb using a tourniquet and injecting adenovirus into the blood vessel using a perfusion pump.

Applicants argue applicants' invention teaches preventing outflow (pg 7 of applicants' brief, 2nd full ¶). Applicants' argument is not persuasive. The claims are not limited to preventing outflow or all blood flow to the limb. The claims encompass occluding a blood vessel of a limb using a tourniquet and injecting adenovirus into the blood vessel using a perfusion pump, which did not result in "delivery" of adenovirus to skeletal muscle cells as taught by Milas.

Applicants argue they delivered polynucleotides to skeletal muscle cells of the limb, which is adequate to overcome the teachings of Milas. Applicants' argument is not persuasive. The claims encompass occluding a blood vessel of a limb using a tourniquet and injecting adenovirus into the blood vessel using a perfusion pump, which did not result in "delivery" of adenovirus to skeletal muscle cells as taught by Milas.

c) **Enablement of polynucleotides encoding proteins in the absence of a promoter**

Applicants argue a promoter is not required to delivery a polynucleotide as claimed. Applicants' argument is not persuasive. First, the claims are only being examined as they relate to polynucleotides encoding proteins and not blocking polynucleotides. In the restriction requirement sent 1-8-02 polynucleotides encoding proteins were separated from those that blocked protein expression, i.e. antisense RNA. Applicants' did not distinctly or specifically point out any supposed errors in the restriction requirement, and the election was treated without traverse (pg 2 of office action sent 7-30-02). Therefore, the claims should be limited to polynucleotides encoding proteins. Second, the specification only describes polynucleotides encoding proteins as being operably linked to a promoter. This is found in the Factor IX gene in example IX and the marker genes described throughout the examples. Therefore, the claims should be limited to a nucleic acid sequence encoding a protein operably linked to a promoter.

Applicants argue the polynucleotide does not have to encode a protein because it can encode an RNA molecule that is not translated into protein but has a cellular function itself. Applicants' argument is not persuasive. The claims are only being examined as they relate to polynucleotides encoding proteins and not blocking polynucleotides. In the restriction requirement sent 1-8-02 polynucleotides encoding proteins were separated from those that blocked protein expression, i.e. antisense RNA. Applicants' did not distinctly or specifically point out any supposed errors in the

restriction requirement, and the election was treated without traverse (pg 2 of office action sent 7-30-02). Therefore, the claims should be limited to polynucleotides encoding proteins.

d) **Enablement of delivering a polynucleotide encoding a protein to skeletal muscle cells without obtaining expression**

Applicants argue the polynucleotide does not have to be expressed because it can encode an RNA molecule that is not translated into protein but has a cellular function itself. Applicants' argument is not persuasive. The claims are only being examined as they relate to polynucleotides encoding proteins and not blocking polynucleotides. In the restriction requirement sent 1-8-02 polynucleotides encoding proteins were separated from those that blocked protein expression, i.e. antisense RNA. Applicants' did not distinctly or specifically point out any supposed errors in the restriction requirement, and the election was treated without traverse (pg 2 of office action sent 7-30-02). Therefore, the claims should be limited to obtaining protein expression.

The declaration by Jon A. Wolff filed 6-14-06 has been considered. The declaration was not argued under any specific rejection in the response filed 6-14-06 or in any of the appeal briefs. It is assumed the declaration was intended to address the enablement rejections; however, it fails to overcome the enablement rejection. The declaration does not address how to apply a tourniquet to a limb, insert an injection devise into the limb proximal to the tourniquet, and inject a polynucleotide distal to the tourniquet. The declaration does not address delivering adenoviral vectors. The declaration does not disclose the structural elements in the vector; therefore, the

declaration does not enable using polynucleotides encoding a protein in the absence of a promoter in the methods claimed. The declaration does not address the purpose of merely delivering a polynucleotide to skeletal muscle cells without obtaining protein expression as claimed. Overall, the declaration fails to correlate to the four points of the enablement rejection.

III. **Indefiniteness**

a) **Indefiniteness of "impeding blood flow to the surface of the skin"**

Applicants argue the examiner has taken the phrase out of context. Applicants' argument is not persuasive. While the examiner did not type out all of claim 1, step b), the phrase was considered in context of step b). Applicants argue the phrase is taken directly from pg 5, lines 13. Applicants' argument is misplaced under 112/2nd because it does not address how the metes and bounds of the phrase are made clear by the specification. The specification contemplates applying a cuff or tourniquet to the skin not impeding blood flow to the skin as now claimed. Furthermore, it is unclear if the "surface of the skin" is limited to the epidermis or encompasses subcutaneous levels of the skin. Overall, it cannot be determined when a devise impedes "blood flow to the surface of the skin" as claimed.

b) **Indefiniteness of applying "sufficient pressure" to "occlude blood flow to said limb"**

Applicants argue cuffs and tourniquets are described in the specification as occluding blood flow and that pg 5, lines 15-19, describes how to use these devises to occlude blood flow to the limb. Applicants argue the plod pressure varies from person to person

and one of skill would know when blood flow had been occluded using a stethoscope. Applicants' arguments are not persuasive. While the specification teaches a cuff or tourniquet may be applied to the skin to occlude blood flow, the amount of pressure required to occlude blood flow as claimed is unclear. Specifically, it is unclear if the mere application of the cuff or tourniquet is "sufficient pressure" "to occlude blood flow to said limb", if any external pressure applied to the cuff or tourniquet is "sufficient pressure" "to occlude blood flow to said limb" or if a specific amount of external pressure applied to the cuff or tourniquet is "sufficient pressure" "to occlude blood flow to said limb" as claimed. For example, it is unclear if the claim encompasses applying the cuff without inflating the cuff, applying the cuff while barely inflating the cuff or if the claim is limited to applying the cuff and inflating it to a certain pressure. Without such guidance, one of skill would not be able to determine when they were infringing on the claim.

c) **Lack of antecedent basis for "said occlusion"**

Applicants argue "said occlusion" in step d) of claim 1 has antecedent basis in the phrase "to occlude blood" in step c) and provide a definition of "occlusion." Applicants' arguments are not persuasive. Literal antecedence is required when using the term "said" and "to occlude" is not literal antecedence for an "occlusion" as claimed. Therefore, "said occlusion" in step d) lacks antecedent basis. Consider especially the fact that the "to occlude blood flow" is an intended use in step c) and may not occur. Overall, claim 1 does not have an active step (performing the action) of occluding blood flow or making an "occlusion" in a blood vessel; therefore, the phrase "said occlusion" lack antecedent basis.

d) **Incomplete method steps in claims 1 and 39**

Applicants argue they have addressed the fact that the claim does not recite all the steps of the method in response to rejections under 112/1st paragraph. Applicants' argument is not persuasive. Such arguments cannot be found. Assuming the arguments are under the response to the enablement rejection, nowhere does the response address the lack of clarity in claim 1 caused by merely claiming delivery of DNA without claiming expression or a therapeutic effect. Applicants argue gene therapy references known in the art describe the benefits of delivering polynucleotides to cells in vivo. Applicants' argument is not persuasive because the claim does not require obtaining a therapeutic effect and because the art at the time of filing taught that it was unpredictable whether a therapeutic effect would occur. Thus, it is not clear that the claim encompasses obtaining a therapeutic effect. Applicants point to pg 2, lines 29-30, pg 6, line 18-29, and pg 7, line 28, through pg 8, line 14, which teach altering the endogenous properties of the cell, blocking gene expression, cleaving cellular RNA, blocking transcription, binding to cellular proteins, expressing proteins, or obtaining therapeutic effects. Applicants' arguments are not persuasive. The claim does not require altering the endogenous properties of the cell, blocking gene expression, cleaving cellular RNA, blocking transcription, binding to cellular proteins, expressing proteins, or obtaining therapeutic effects. The art at the time of filing taught that it was unpredictable whether the desired effect would occur. The only effect obtained by applicants was expressing a marker protein, which in and of itself does not have any disclosed use. Thus, it is not clear that the claim encompasses altering the endogenous

properties of the cell, blocking gene expression, cleaving cellular RNA, blocking transcription, binding to cellular proteins, or obtaining therapeutic effects.

e) **Indefiniteness of the phrase "wherein function of the limb is not affected by inserting the injector, applying pressure to the vessel, and injecting the solution"**.

Applicants argue the phrase reflects one of the novel aspects of the invention and is important to applicants. Applicants' argument is not persuasive. The phrase is a functional limitation of the overall method and is not an "active step" as written.

IV. **102 over Milas**

Applicants argue the DNA of Milas is not delivered to the skeletal muscle cells in the leg because an inflammatory response in skeletal muscle cells merely indicates presence of immune cells and because Milas did not obtain β-gal staining in skeletal muscle cells. Applicants' argument is not persuasive. First, the claim does not require obtaining expression of a protein. Next, while Milas did not obtain detectable β-gal staining in skeletal muscle cells, the fact that Milas described thorough leakage of blood out of the blood vessels into the entirety of the leg (pg 2200, Fig. 3) reasonably implies that adenovirus also leaked out of the blood vessels into the entirety of the leg. The fact that Milas described inflammatory infiltrates in skeletal muscle (pg 2201, col. 2, lines 23-26) reasonably implies the movement of immune cells into the skeletal muscle to target beyond mere leakage of immune cells. Blood leaking out of the blood vessels into the entirety of the leg would enter the skeletal muscle only if a foreign substance was present. The patent office does not have the means to prove the adenovirus that failed to cause expression in skeletal muscle of Milas was at least "delivered" to skeletal

muscle cells as claimed. However, without evidence to the contrary, the leakage of blood throughout the entirety of the leg in Fig. 3 combined with the inflammatory infiltrates in skeletal muscle are adequate to reasonably conclude that the adenovirus was at least delivered to skeletal muscle cells as claimed despite failing to obtain expression.

Applicants argue Fig. 3 does not show that blood cells leaked out of the vasculature. Applicants' argument is not persuasive. Assuming *arguendo* that the adenovirus did not leak out of the vasculature, Fig. 3 shows the blood was distributed throughout the entirety of the leg via the vasculature; therefore, one of ordinary skill could reasonably conclude that the adenovirus passed throughout the entirety of the vasculature of the leg, including the muscular branches of the femoral artery. Therefore, adenovirus passed through the vasculature of the skeletal muscle and was in contact with skeletal muscle cells, which meets the limitation of "delivering the polynucleotides to said skeletal muscle cells" as claimed.

Applicants argue Milas allowed for inflow of fluid into the leg using the perfusion pump at a rate of 2.4 ml per minute and for outflow of fluid out of the leg. Applicants' arguments are not persuasive. Claim 1 and 39 merely require occluding blood flow to said limb, which is equivalent to applying a tourniquet as described by Milas because the tourniquet occludes blood from flowing into or out of the leg. The claims do not require occluding all blood flow. The claims also use open language and encompass occluding blood flow using a tourniquet while using a perfusion pump.

Applicants argue the method of Milas is different than the method used by applicants because Milas used perfusion to allow outflow of blood from the leg. Applicants argue the claims "inherently results in no outflow". Applicants' arguments are not persuasive. The argument that the claims inherently result in no outflow is unfounded. The tourniquet described by Milas most definitely occludes inflow and outflow of blood to the leg. The claims encompass a tourniquet applied to the limb while a perfusion pump is applied. The claims do not exclude allowing outflow of blood using a perfusion pump while applying a tourniquet that occludes blood flow. The claims are not limited to occluding all outflow of blood from the limb.

V. **Double Patenting**

Provisional obviousness type double patenting rejection of claims 1-3 and 6-9, 11-14, 16-22, 24-26, 28-31, 34-36 and 39 over claims 1-3, 6, 7, 11, 12, 16-20, 24, 25, 28-31, 34-36 and 39-42 of copending Application No. 09/707117.

Applicants' willingness to file a terminal disclaimer as necessary was acknowledged in the final office action.

Applicants argue in the brief that '117 and the instant application were owned by the same person or subject to an obligation of assignment to the same person. Therefore, applicants conclude, the rejection is obviated. Applicants' argument is not persuasive. The same inventive entity cannot have two patents for essentially the same invention.

(11) Related Proceeding(s) Appendix

No decision rendered by a court or the Board is identified by the examiner in the Related Appeals and Interferences section of this examiner's answer.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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